974-85 The Reduction in Rate of Peri-angioplasty Myocardial Infarction After Treatment with IIb/IIIa Receptor Antagonists is Dependent on MI Definition

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The effectiveness of GP IIb/IIIa receptor antagonists is often assessed using a composite endpoint of death, myocardial infarction (MI), and urgent revascularization. Blinded committees have used clinical events (chest pain and ECG changes), and quantitative but unstandardized enzyme criteria (often clinically silent) to determine MI.

RESTORE was a 2,139 pt comparison of tirofiban vs placebo in "high risk" angioplasty. The definition for MI was clinical (pain, ECG and enzymes) or CK-MB elevation (≥3× nl in hospital or 2× nl from discharge to 30 days). There was a 26% reduction (p = 0.113) in MI in the tirofiban group. If higher enzyme levels had been used, the effect of tirofiban increased: CK-MB ≥ 3× elevated = 36% reduction (p = 0.04); ≥4× elevated = 39% (p = 0.04); ≥4× elevated = 39% (p = 0.04); ≥5× elevated = 41% (p = 0.04); ≥10× elevated = 56% (p = 0.019). Using the investigator clinical diagnosis, MI reduction was 27% (p = 0.246). Each of these alternative MI definitions also influenced the composite primary endpoint: 16% reduction using protocol definition (p = 0.16); 19% using CK-MB ≥3× (p = 0.093); and 20% using investigator diagnosis of MI (p = 0.074).

These findings suggest that the outcome of GP IIb/IIIa trials having MI as an endpoint can be markedly influenced by the enzyme criteria for MI. The clinical outcome associated with the enzyme levels needs definition so a meaningful standard can be adopted.

974-86 Ticlopidine Potentiates Abciximab's Ability to Inhibit ADP-induced Platelet Aggregation In Vitro

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Abciximab (7E3) is indicated in pts undergoing high risk PTCA. Increasingly such pts receive intracoronary stents and are also treated with the antiplatelet drug ticlopidine (T) which depresses platelet function by inhibiting ADP-mediated aggregation. The combined interaction between these agents is unknown. We studied this interaction *in vitro* in 10 pts receiving aspirin and T (500 mg immediately after stenting and continued at 250 mg BID) and in 3 pts treated with aspirin only after PTCA. At baseline, concentrations of ADP producing the maximal aggregation response for each individual patient were determined in citrate-anticoagulated platelet-rich plasma (range 5–8 μM). Using these agonist concentrations, IC50s for exogenously added 7E3 were determined at baseline, 18–36 hours, and 7–10 days. IC50s (μg/mL) of 7E3 were:

Baseline	18–36 H	7–10 D
1.06 ± 0.26	0.98 ± 0.2	0.70 ± 0.13

P (Baseline – 18–36 H) = 0.12; P (Baseline – 7–10 D) < 0.003

In pts receiving aspirin alone, there were no differences between either time point and baseline.

These findings indicate a subtle interaction between *in vivo* T and abciximab's ability to inhibit ADP-induced platelet aggregation after the first week of treatment but not the first day. Clinical evaluations in pts treated with both agents will define the combined pharmacodynamic effects of both abciximab and ticlopidine.

974-87 The Antibody Fragment c7E3 (ReoPro®) Binds to Activated and Nonactivated Mac-1 on Granulo- and Monocytes and Blocks Mac-1-mediated Cell Adhesion and Aggregation

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The humanized Fab fragment c7E3 binds to the platelet integrin GPIIb/IIIa and thereby blocks fibrinogen binding to platelets. The clinical benefits of c7E3 are mainly attributed to the inhibition of platelet aggregation and adhesion. Since fibrinogen is not only a ligand for GPIIb/IIIa but also for the leukocyte integrin Mac-1, we evaluated whether c7E3 is able to block Mac-1 (CD 11b/CD 18) with similar characteristics as c7E3 blocks GPIIb/IIIa.

The binding of c7E3 and fibrinogen to Mac-1 was evaluated with flow cytometry of whole blood samples. c7E3 binds to resting granulo- and monocytes (half maximal: 1, maximal: 10 μg/ml). This binding can be inhibited by monoclonal antibody (mAb) 44 (anti-CD11b, 10 μg/ml). A comparison with the mAb 7A10 (specific for a Mac-1 activation neoepitope) demonstrates similar binding of c7E3 on activated and nonactivated Mac-1. Flow cytometry with a chicken anti-fibrinogen mAb reveals inhibition of fibrinogen binding on Mac-1 by c7E3 (half maximal: 2, maximal: 10 μg/ml c7E3). Aggregation of the PMA-stimulated human monocytic cell line U937 is totally blocked with 10 μg/ml of c7E3. Cell adhesion of U937 on fibrinogen is blocked by 77 ± 5 percent (P < 0.002) with 10 μg/ml of c7E3.

Conclusions: c7E3 binds to the activated and nonactivated Mac-1 with similar affinity. Thus, fibrinogen binding to Mac-1, and Mac-1-mediated cell adhesion and aggregation are effectively inhibited by therapeutic concentrations of c7E3. The blockade of Mac-1 may contribute to the short term but even more to the long-term clinical benefits of c7E3.

974-88 Platelet Aggregation and Fibrinogen Binding in Patients Treated with Integrelin and Abciximab During Coronary Angioplasty

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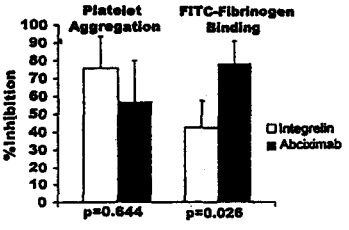
Inhibition of platelet aggregation (PA) by glycoprotein (GP) IIb/IIIa receptor antagonists reduces abrupt closure and myocardial infarction after coronary angioplasty (PTCA). We compared the effects of Integrelin and Abciximab on ADP-stimulated (20 μm) PA and on fibrinogen binding to activated GP IIb/IIIa receptors using fluorescein isothiocyanate fibrinogen (FITC-FGN). We studied 13 controls, 25 IMPACT-II patients treated with Integrelin, and 14 patients treated with Abciximab during PTCA. Integrelin dosing was based on *in vitro* assays of Integrelin-induced inhibition of PA, which we have previously shown is potentiated when citrate-containing samples are used. PA and FITC-FGN binding did not differ among the three groups at baseline and did not change in the control group following PTCA. There was no statistical difference in the inhibition of PA between Integrelin and Abciximab. However, inhibition of FITC-FGN binding was significantly greater with Abciximab than Integrelin (78 vs 42%, p = 0.026).



This difference may be due to underdosing of Integrelin in the IMPACT-II study or to inherent differences in the two agent's binding and/or affinity for the GP IIb/IIIa receptor.

974-89 Use of Abciximab (ReoPro®) is Not Associated With an Increase in the Risk of Stroke: Overview of Three Randomized Trials

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Abciximab (ReoPro) is a potent glycoprotein IIb/IIIa receptor antagonist used to prevent ischemic complications of percutaneous intervention. Because of its antithrombotic effect, concern exists about the effect of abciximab on the risk of stroke. Three large randomized clinical trials have randomly allocated patients to treatment with abciximab. All trials used concomitant heparin, although the dose in EPIC and CAPTURE was higher than the dose in EPILOG. The duration of the infusion varied, but all trials used a bolus of 0.25 mg/kg of abciximab followed by an infusion of 0.10 μg/min. The number of strokes in each trial are shown.

	EPIC		CAPTURE		EPILOG		TOTAL	
	P	A	P	A	P	A	P	A
N	681	678	630	623	914	1811	2225	3112
Non-hem	2	2	2	0	0	2	4	3
Hem	2	2	1	0	0	4	3	6
Unk	0	0	0	1	0	0	0	1
Any	4	4	3	1	0	6	7	10

All p values >0.45; P = placebo, A = abciximab, Non-hem = non-hemorrhagic stroke, Hem = hemorrhagic stroke, Unk = unknown etiology.

When used according to protocol, there is no evidence of a clinically meaningful increase in stroke rate with the use of abciximab (0.31% with placebo and 0.35% with abciximab).

TUESDAY POSTER